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Original Article

Efficacy and Safety of a Novel Tapered-Tip Sheath System for Biliary-Lesion Tissue Sampling: A Randomized Controlled Trial

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Background/Aims: Pathological evaluation is crucial for diagnosing biliary lesions and determining appropriate treatment strategies. However, tissue sampling via the transpapillary route can be difficult. In this study, we aimed to assess the efficacy and safety of a novel tapered-tip sheath system for tissue sampling from biliary strictures.

Methods: This single-center, randomized, parallel-group clinical trial included patients aged 20 to 85 years admitted to Kyoto University Hospital for biliary strictures. The patients were randomly assigned (1:1) to a new or conventional method group. The primary outcome was technical success of biopsy at the target bile duct using the assigned method, as determined in accordance with the intention-to-treat principle. Adverse events were assessed in all eligible patients.

Results: Fifty-six patients were assessed for eligibility between September 2020 and March 2023; 50 patients were enrolled. The patients were randomly divided into the new (n=25) method group and the conventional (n=25) method group. Technical success was achieved in 96.0% (24/25) and 48.0% (12/25) of patients in the new and conventional method groups, respectively (risk ratio, 2.00; 95% confidence interval [CI], 1.32 to 3.03; risk difference, 48.0%; 95% CI, 27.0% to 69.0%; p<0.001). Adverse events occurred in 4.0% (1/25) and 36.0% (9/25) of patients in the new and conventional method groups, respectively (risk ratio, 0.11; 95% CI, 0.02 to 0.81; risk difference, –32.0%; 95% CI, –52.3% to –11.7%; p=0.005).

Conclusions: The novel tapered-tip sheath system is a promising option for precisely and safely delivering biopsy forceps to target sites, thereby facilitating the diagnosis of biliary strictures. **(Gut Liver 2025;19:136-144)**

Key Words: Bile ducts; Bile duct neoplasms; Biopsy; Cholestasis; Intention to treat analysis

INTRODUCTION

Despite recent advances in diagnostic imaging, pathological evaluation based on tissue sampling remains crucial for diagnosing biliary lesions and determining treatment strategies.[1-3] Neglecting pathological evaluation in benign cases may result in unnecessary invasive procedures (e.g., liver resections).[1] Tissue sampling from the biliary tract often involves transpapillary approaches, primarily through fluoroscopy-guided forceps biopsy and peroral cholangioscopy (POCS)-guided biopsy.[4] POCS-guided biopsy allows direct observation but has limited applicability owing to the required skill, associated costs, and preparation requirements (including endoscopic sphincterotomy [EST]) with bleeding risks.[5-8] Therefore, fluoroscopy-guided forceps biopsy remains the standard for sampling bile duct tissue.[2] However, it presents several challenges, including difficulty in directly inserting the forceps into the bile duct and selecting the bile duct.[9]

Furthermore, both methods have unsatisfactory diag-

nostic sensitivity and carry procedural risks. Reportedly, fluoroscopy- and POCS-guided forceps biopsies have pooled diagnostic sensitivities of 48.1% and 60.1%, respectively.[5,10] Moreover, these prior reports have focused on cases, in which biopsy forceps were successfully delivered to target sites, rather than conducting intention-to-treat analyses of patients in whom transpapillary bile duct biopsies were attempted.[11]

Regarding adverse events, fluoroscopy-guided forceps biopsy potentially carries the risk of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) due to overloading of the duodenal papilla or accidental forceps insertion into the pancreatic duct. Meanwhile, POCS-guided biopsy requires preprocedural preparation, including EST, which poses a risk of bleeding or perforation.[7,8] Notably, many studies have investigated the association between transpapillary procedures (e.g., biliary cannulation or stenting) and PEP;[7,8,12] however, few have reported on adverse events specific to transpapillary bile duct biopsies.[13]

An ideal transpapillary bile duct biopsy should allow safe and adequate tissue sampling at various target bile ducts. We developed a novel tapered-tip sheath system (EndoSheather; Piolax Medical Devices, Kanagawa, Japan) (Fig. 1) that allows the delivery of standard-sized biopsy forceps to various target bile ducts, ranging from the extrahepatic to the intrahepatic bile duct.[14] This device has a coaxial two-layer structure: (1) an inner catheter with a dilator function owing to its tapered tip, and (2) an outer sheath that serves as a conduit to easily guide the biopsy forceps to the target bile duct. Additionally, this system prevents direct and frequent contact between the biopsy forceps and duodenal papilla, as well as avoids the risk of misinsertion of the biopsy forceps into the pancreatic duct, thus minimizing adverse events (such as PEP) and enhancing procedural safety. Our previous retrospective study supported the usefulness of this device.[14,15] In this study, we aimed to prospectively evaluate the efficacy and safety of this device in transpapillary biliary stricture biopsies, following the intention-to-treat principle.

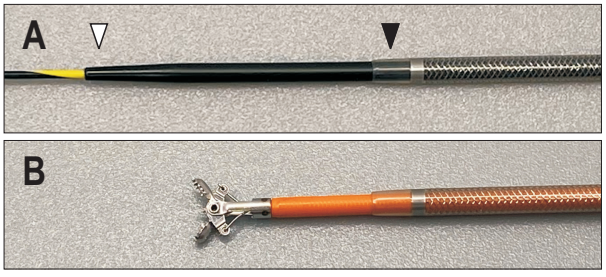

Fig. 1. The novel tapered-tip sheath system. (A) The novel tapered-tip sheath system has a coaxial two-layer structure consisting of an inner catheter that functions as a dilator due to its tapered tip (white arrowhead) and an outer sheath that serves as a conduit for the biopsy forceps (black arrowhead). (B) The loading of biopsy forceps into in the outer sheath after the removal of the inner catheter.

MATERIALS AND METHODS

1. Study design and participants

This randomized, parallel-group clinical trial recruited patients with undiagnosed biliary strictures at Kyoto University Hospital between September 2020 and March 2023. The inclusion criteria were as follows: presence of histopathologically undiagnosed biliary stricture, possibility of transpapillary bile duct approach using a side-viewing endoscope, age ≥20 years, and provision of written informed consent. The exclusion criteria were biliary stricture already diagnosed histopathologically, poor general condition (e.g., severely impaired cardiac or respiratory function), surgically altered anatomy other than Billroth I reconstruction or inability to access the duodenal papilla, unsuccessful biliary cannulation, history of EST, and patients deemed inappropriate by investigators. This study was approved by the Institutional Ethical Review Board of Kyoto University Hospital (approval number: Y0057) and is available on the Japan Registry for Clinical Trials website (jRCT1052200051). This study was performed according to the principles embodied in the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research Involving Human Subjects. All participants provided written informed consent before study enrolment.

2. Randomization and masking

After successful biliary cannulation, the enrolled patients were randomly assigned in a 1:1 ratio to the new or conventional method group through computer-generated randomization (Fig. 2). Stratified block randomization based on biliary stricture site (intrahepatic, perihilar, and distal bile ducts) was employed. The assigned methods were placed in sealed opaque envelopes with sequential numbers, prepared by a third-party analyst, and stored on a lockable shelf in a separate room. Independent physicians sequentially opened these envelopes corresponding to the stricture site and determined the allocation. The patients, outcome assessors, and data analysts were blinded to the assigned methods, and the endoscopists were blinded to the primary outcome but not to the assigned methods.

3. Procedure

The procedures were performed by endoscopists with 1 to 18 years of endoscopic experience who were blinded to

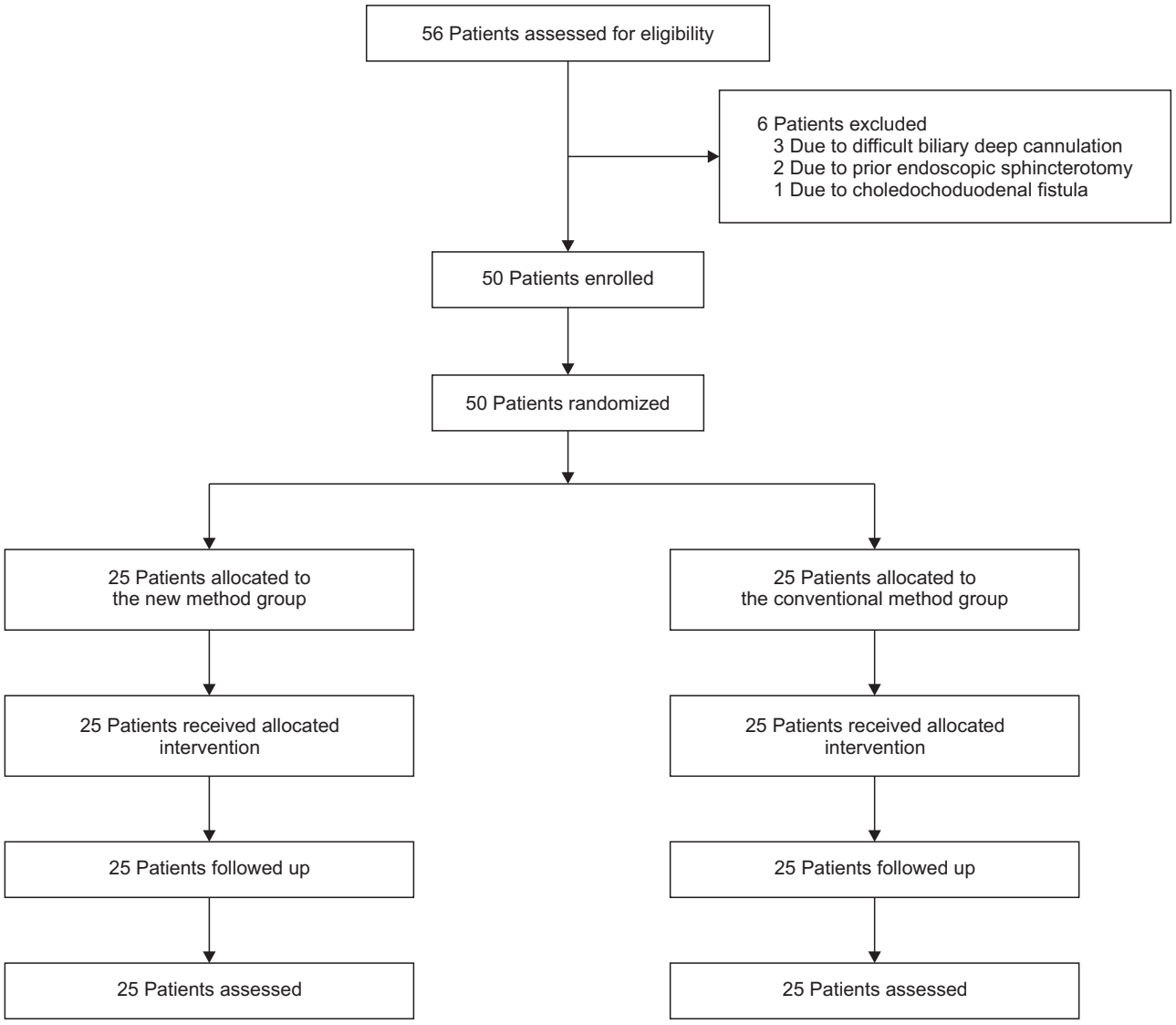

Fig. 2. The Consolidated Standards of Reporting Trial flow diagram showing enrolment, allocation, and analyses performed in this study.

the primary outcome and were simply instructed to perform three bile duct biopsies. ERCP was conducted using a side-viewing duodenoscope (TJF-260V or TJF-Q290V; Olympus Medical Systems, Tokyo, Japan) following standard procedures. Anatomical features and biliary strictures were fluoroscopically observed after biliary cannulation. A guidewire was placed through the stricture, and the patients were randomly allocated to either the new or the conventional method group. In the new method arm, the novel device was inserted into the target bile duct over the guidewire. After removing the guidewire and inner catheter, biopsy forceps (Radial Jaw 4P; Boston Scientific Japan, Tokyo, Japan) were delivered to the target site through the outer sheath for tissue collection, as previously reported.[14,15] In the conventional method arm, the biopsy forceps were directly inserted into the bile duct, and tissue sampling was performed at the target site under fluoroscopy. Three biopsy specimens were acquired from the biliary stricture to improve diagnostic sensitivity and accuracy.[16] The obtained samples were grossly confirmed by healthcare providers, fixed with formalin, and subsequently sent to the department of pathology for histological evaluation. When an assigned method failed, crossover to another method was permitted from an ethical perspective at the endoscopist's discretion. Finally, a nasobiliary drainage tube was placed to monitor biliary hemorrhage and prevent biliary obstruction by clots. EST was not performed in this clinical trial until a diagnosis of benign or malignant disease was confirmed. The attending physicians monitored the patients for at least 1 week to detect any adverse events associated with the biopsy procedure.

4. Outcome measures

The primary outcome measure was the technical success of the biopsy at the target bile duct using the assigned method. At least three samples are needed to improve the low sensitivity of transpapillary forceps biopsy.[16] PEP is a critical adverse event in transpapillary procedures; however, reports of adverse events associated with bile duct biopsies remain limited.[13] Therefore, we used the risk of PEP development following biliary cannulation as a reference.[7,8] Biliary cannulation requiring >15 minutes is a risk factor for PEP development.[12] Considering these factors, technical success was defined as performing three consecutive biopsies within 5 minutes each, aiming for completion within 15 minutes, prioritizing patient safety. All other instances were deemed failures. Independent physicians or nurses assessed technical success by grossly confirming the presence of tissue fragments. When an assigned method failed, crossover to another method was allowed owing to ethical reasons. However, following the intention-to-treat principle, the result was not considered successful even if the switched method was effective.

The secondary outcome measures were adequate tissue sampling, total biopsy time, and adverse events. Three experienced cytopathologists with expertise in pancreaticobiliary diseases and blinded to the allocation assessed the biopsy specimens. Tissue sampling was considered adequate if at least one of the three samples obtained was suitable for pathological evaluation. Biopsy time was defined as the time from when the biopsy forceps reached the duodenal papilla to tissue collection and forceps removal. The total biopsy time was calculated as the sum of the durations of each biopsy and was measured from recorded endoscopy videos by a clinical nurse blinded to the study outcome. Adverse events were determined by attending physicians blinded to the allocation following consensus criteria.[7,8]

Further, prespecified subgroup analyses stratified by the biliary stricture site were performed. *Post hoc* analyses were performed for patients with technical success using the assigned method and those with technical failure.

5. Statistical analyses

The target sample size was calculated based on the primary outcome measure. Assuming a technical success rate of 90% for the new method and 50% for the conventional method from our preliminary study,[14] we estimated a sample size of 44 patients (22/group) to detect differences with 85% power and a 5% significance level on the chi-square test. To accommodate possible dropouts (10%), the total sample size was set at 50 patients. The sample size was calculated using power analysis and sample size (NCSS; LLC, Kaysville, UT, USA).

Quantitative variables were presented as medians with interquartile ranges and categorical variables as absolute numbers with percentages. Binary outcomes were compared using the chi-square test, and both risk ratios (RRs) and risk differences (RDs) with 95% confidence intervals (CIs) were estimated. Continuous outcomes were compared using the Wilcoxon/Mann-Whitney test, and mean differences with 95% CIs were calculated. A data analyst masked to the assigned methods and uninvolved in the procedures conducted the analyses following the intention-to-treat principle. All authors had access to the study data and reviewed and approved the final manuscript. All statistical analyses were performed using Stata 17 (StataCorp, College Station, TX, USA). A p-value <0.05 was considered statistically significant.

RESULTS

1. Patient characteristics

Among 56 patients evaluated for eligibility between September 7, 2020, and March 15, 2023, 50 patients were

Table 1. Baseline Characteristics of the Intention- to-Treat Population

Characteristic	New method (n=25)	Conventional method (n=25)
Age, yr	74 (64–77)	70 (64–79)
Sex		
Male	19 (76)	16 (64)
Female	6 (24)	9 (36)
Stricture site		
Intrahepatic	4 (16)	2 (8)
Perihilar	14 (56)	15 (60)
Distal	7 (28)	8 (32)
Diagnosis		
Intrahepatic cholangiocarcinoma	3 (12)	1 (4)
Perihilar cholangiocarcinoma	9 (36)	13 (52)
Distal cholangiocarcinoma	5 (20)	6 (24)
Gallbladder carcinoma	4 (16)	2 (8)
Pancreatic cancer	2 (8)	2 (8)
Others	2 (8)	1 (4)
Tumor (T) stage		
Tis	2 (8)	1 (4)
T1	9 (36)	4 (16)
T2a+T2b	6 (24)	7 (28)
T3	4 (16)	9 (36)
T4	4 (16)	4 (16)
CEA, ng/mL	4.3 (3.5–8.9)	3.2 (2.3–5.8)
CA19-9, U/mL	39.6 (16.4–228.7)	62.0 (18.4–259.0)
Cannulation time, min	8 (2–14)	7 (4–15)
Total procedure time, min	40 (30–64)	43 (34–77)

Data are presented as the median (interquartile range) or number (%).
T stage is based on the Union for International Cancer Control 8th edition.
CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

included (25 patients/group). All patients completed the study and had complete data (Fig. 2). Table 1 summarizes the baseline patient characteristics. There were no significant differences in patient characteristics.

2. Primary and secondary outcomes

The study outcomes are summarized in Table 2. Technical success was achieved in 96.0% (24/25) and 48.0% (12/25) of patients in the new and conventional method groups, respectively (RR, 2.00; 95% CI, 1.32 to 3.03; RD, 48.0%; 95% CI, 27.0% to 69.0%; p<0.001). Prespecified subgroup analyses by biliary stricture site showed that the new method achieved higher technical success in the perihilar and distal bile ducts, compared with the conventional method (Table 3). The reasons for technical failure included poor sedation impeding the examination (n=1) in the new method group and difficulty in inserting biopsy forceps into the bile duct (n=9) or in guiding the forceps to the target site post-insertion (n=4) in the conventional method group.

Adequate tissue samples were obtained in 88.0% (22/25) and 44.0% (11/25) of patients in the new and conventional method groups, respectively (RR, 2.00; 95% CI, 1.26 to 3.19; RD, 44.0%; 95% CI, 20.7% to 67.3%; p=0.001). For stricture site, the new method yielded higher rates of adequate tissue sampling in the perihilar and distal bile ducts, compared with the conventional method. The total biopsy time was shorter with the new method than with the conventional method (110.5 seconds [90.5–213.5] vs 236 seconds [187.5–320.0]; mean difference: –95.3 [–167.6 to –23.1]; p=0.005). Particularly, the time was shorter for the perihilar bile duct with the new method versus the conventional method. Adverse events occurred in 4.0% (1/25) and 36.0% (9/25) of patients in the new and conventional method groups, respectively (RR, 0.11; 0.02 to 0.81; RD, –32.0%; 95% CI, –52.3% to –11.7%; p=0.005). One patient in the new method group developed mild PEP and eight in the conventional method group developed PEP, including one patient with severe PEP. Bleeding after biopsy occurred in one patient in the conventional method group.

3. *Post-hoc* analyses

Post-hoc analyses of patients with technical success in each group indicated adequate tissue samples in 91.7% of cases for both the new (22/24) and conventional (11/12) methods (Table 4). Regarding unsuccessful cases, no crossover was observed in the new method group, whereas 12 patients were crossed over from the conventional method to the new method. Of these 12 patients, technical success was achieved in 11, and adequate tissue samples were obtained in 10.

Table 2. Study Outcomes

Variable	New method (n=25)	Conventional method (n=25)	p-value	Risk ratio (95% CI)	Risk difference, % (95% CI)	Mean difference (95% CI)
Technical success	24 (96)	12 (48)	<0.001	2.00 (1.32–3.03)	48.0 (27.0 to 69.0)	
Reasons for failure						
Difficulty in inserting forceps	0	9				
Difficulty in guiding forceps to the target site	0	4				
Poor sedation	1	0				
Adequate tissue sampling	22 (88)	11 (44)	0.001	2.00 (1.26–3.19)	44.0 (20.7 to 67.3)	
Total biopsy time, sec	110.5 (90.5–213.5)	236.0 (187.5–320.0)	0.005			–95.3 (–167.6 to –23.1)
Adverse events						
Total	1 (4)	9 (36)	0.005	0.11 (0.02–0.81)	–32.0 (–52.3 to –11.7)	
Acute pancreatitis	1	8				
Mild	1	7				
Moderate	0	0				
Severe	0	1				
Bleeding	0	1				
Crossover	0	12 (48)	<0.001			

Data are presented as number (%) or median (interquartile range).
CI, confidence interval.

Table 3. Subgroup Analyses for Biliary Stricture Site

Variable	New method (n=25)	Conventional method (n=25)	p-value
Technical success			
Intrahepatic	3/4 (75.0)	0/2 (0)	0.083
Perihilar	14/14 (100)	9/15 (60.0)	0.008
Distal	7/7 (100)	3/8 (37.5)	0.010
Adequate tissue sampling			
Intrahepatic	2/4 (50.0)	0/2 (0)	0.220
Perihilar	13/14 (92.9)	8/15 (53.3)	0.017
Distal	7/7 (100)	3/8 (37.5)	0.010
Total biopsy time, sec			
Intrahepatic	238 (220–270)	-	NA
Perihilar	106 (84–159)	221 (185–331)	0.006
Distal	107 (87–191)	251 (191–262)	0.110

Data are presented as number/number (%) or median (interquartile range).
NA, not available.

Table 4. *Post-hoc* Analyses for Technical Success and Failure Cases

Variable	New method (n=25)	Conventional method (n=25)
Technical success cases	24	12
Adequate tissue sampling	22/24 (91.7)	11/12 (91.7)
Technical failure cases	1	13
Crossover cases	0	12
Technical success after crossover	-	11/12 (91.7)
Reasons for technical failure		
Difficulty in guiding forceps to the target site	-	1
Adequate tissue sampling after crossover	-	10/12 (83.3)

Data are presented as number or number/number (%).

DISCUSSION

Most previous reports on fluoroscopy-guided transpapillary forceps biopsy focused on the successful insertion of biopsy forceps into the target bile duct but did not address cases of attempted insertion failure or difficulties in guiding the biopsy forceps to the target bile duct.[10,11,15,16] This study analyzed cases of attempted insertion following an intention-to-treat principle and demonstrated superior effectiveness and safety of the novel device over the conventional method for biliary stricture biopsy.

Delivering diagnostic devices to the target site and obtaining adequate tissue samples for histological evaluation are two crucial steps in the pathological assessment of biliary lesions. This study focused on these steps and analyzed technical success as the primary outcome while prioritizing patient safety. The technical success rate was notably higher with the new method than with the conventional method, with the biopsy forceps successfully delivered to the target bile duct in all but one patient who experienced poor sedation. This may be explained by the tapered shape of the novel device, which facilitates passage through the duodenal papilla and access to narrower and curved target bile ducts. Furthermore, the device allows for precise delivery of biopsy forceps to various target bile ducts through the outer sheath after removing the inner catheter.

Conversely, the technical success rate was lower with the conventional method than with the new method, with the forceps successfully inserted in only approximately half of the attempted biopsies. This may be because, in addition to not having the advantages of the novel device, we strictly defined technical success as performing three consecutive biopsies within 5 minutes each, as patient safety was the highest priority. Additionally, biopsy forceps insertion into the bile duct was not possible in nine patients in the conventional method group, and the biopsy forceps could not be delivered to the target bile duct despite successful bile duct insertion in four patients, suggesting that reaching target sites using the conventional method is challenging. Various devices have been reportedly developed to guide the biopsy forceps to the target bile duct. However, they have not gained popularity because of their large diameter or lack of coaxiality, which can cause them to become stuck at the duodenal papilla.[9,17,18]

The rate of adequate tissue sampling, a crucial factor for accurate diagnosis, was also significantly higher in the new method group than in the conventional method group. Navaneethan *et al.*[10] reported a pooled sensitivity of 48.1% for transpapillary bile duct biopsy and 59.4% when combined with brush cytology. Tissue collection volume[19,20] and sample number affect the sensitivity of transpapillary forceps biopsy.[16,21] At least three tissue samples should be collected for accurate diagnosis in fluoroscopy-guided and POCS-guided biopsies.[16,21] The novel device allows the use of larger biopsy forceps, compared with POCS-guided biopsies, and enables multiple samplings through the outer sheath mechanism, which may be advantageous with respect to tissue volume and number, potentially enhancing sampling quality.

The rates of adequate tissue sampling were comparable between the two groups for patients with technical success, suggesting equivalence in sampling quality when technical success was achieved. Considering adequate tissue sampling in the intention-to-treat population, the result indicates that the successful delivery of biopsy forceps to the target bile duct—the first step of bile duct evaluation—is the most critical step in transpapillary forceps biopsy. Furthermore, focusing on the 12 cases of crossover from the conventional to the new method because of technical failure, the biopsy forceps were successfully delivered to the bile duct of interest in 11 out of 12 cases, and adequate

tissue samples were obtained in 10 cases. These results further indicate that the first step of transpapillary forceps biopsy is critical, and the novel device likely facilitates this step. Concurrently, future improvements in the second step of bile duct evaluation, such as the refinement of biopsy forceps, will improve adequate tissue collection. This also suggests that the novel device may be a promising tool for acquiring samples suitable for genetic analysis in the era of precision medicine, particularly for unresectable cholangiocarcinoma.[22]

The novel device enables the two critical steps of transpapillary forceps biopsy—diagnostic device delivery and adequate tissue collection—to be performed within a considerably shorter period. This is because the outer sheath serves as a conduit for the biopsy forceps, resulting in its rapid guidance and tissue collection. Prolonged examinations pose a risk of ERCP-related adverse events, including PEP.[23] In addition, prolonged procedure time entails excessive patient sedation and can result in unwanted radiation exposure to both patients and physicians.[24,25] The novel device allows for a shorter examination time, including biopsy time, thus, potentially reducing the adverse events associated with radiation and sedation, as well as those associated with ERCP.

This study highlights the novel device's role in ensuring safer biopsy procedures and reducing the incidence of PEP, a serious ERCP-related adverse event. The incidence of PEP ranges from 3.5% to 9.7%;[7,8,26,27] however, few studies have described the risk of PEP development specifically for bile duct biopsy procedures.[13] Herein, the incidence of PEP was low (4.0%) and the severity was mild for bile duct biopsies performed using the new method, whereas the incidence was high (36%) for biopsies performed using the conventional method. Considering that there was no difference between the two groups in cannulation time, which is reportedly associated with PEP development,[7,8,12] the difference in the PEP incidence between both methods can be attributed to the bile duct biopsy procedure itself.

The conventional method involves attempting to insert the biopsy forceps, which are thicker and stiffer than the cannula, directly into the bile duct. This not only overloads the duodenal papilla, but also increases the risk of accidentally inserting the biopsy forceps into the pancreatic duct, potentially inducing the development of PEP. Meanwhile, the new method guides the biopsy forceps through the outer sheath of the novel device, thus, avoiding the drawbacks mentioned above and potentially contributing to the reduction in PEP incidence. Furthermore, since transpapillary procedures without EST may be a risk factor for PEP development, EST is often performed in daily practice. However, there is limited evidence on whether the presence on absence of EST truly affects the development of PEP after transpapillary procedures.[13] In this study, we show for the first time scientifically that transpapillary bile duct biopsy without EST is a risk factor for the development of PEP. Conversely, the new method can provide a safe and reliable route for bile duct biopsy even without performing EST, potentially reducing the PEP incidence. Taken together, these results suggest that fluoroscopy-guided forceps biopsy, with the direct insertion of biopsy forceps into the bile duct, may be a risk factor for PEP. On the contrary, biopsy using the novel device can be a useful method for preventing PEP despite the highly technical and invasive nature of bile duct biopsy.

The robustness of this study as a randomized controlled trial, with no patient dropout or missing data, strengthens the evidence supporting the efficacy of the novel device in transpapillary biliary stricture biopsies. However, this study also has some limitations. First, this is a single-center cohort study without EST cases. Therefore, a multicenter trial including EST cases (jRCT1052220103) is underway to validate the study outcomes and assess generalizability in a real-world setting. Second, the patients, outcome assessors, and data analysts were masked to the assigned method. However, the endoscopists were not, although they were simply instructed to obtain three biopsies and were unaware of the primary outcome. Third, we compared the new method with the widely used method of fluoroscopy-guided forceps biopsy but not with POCS-guided biopsy. Future comparative studies with POCS-guided biopsy are warranted to confirm the usefulness of this new method. However, in addition to the skill requirement, POCS-guided biopsy poses several challenges to standardization owing to low diagnostic sensitivity, greater time consumption, adverse events, and high cost.[20,28-30]

In conclusion, the novel tapered-tip sheath system is a promising option for accurately and safely delivering biopsy forceps to the target sites, facilitating adequate tissue sampling and contributing to the challenging diagnosis of biliary strictures.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Study concept and design: H.O., N.U., T.M., H.Y. Data acquisition: H.O., N.U., T.M., M.S., A.F., M.Y., T.K., Y.N., T.M. Data analysis and interpretation: H.O., N.U., T.M. Drafting of the manuscript: H.O., N.U. Critical revision of the manuscript for important intellectual content: H.Y., S.M., E.H., H.S. Statistical analysis: H.Y. Administrative, technical, or material support; Study supervision: A.T., K.T. Approval of final manuscript: all authors.

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